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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/843,126	04/26/2001	Peter C. Astles	CA2413US NP	8340

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EXAMINER	
CHANG, CELIA C	

ART UNIT	PAPER NUMBER
1625	8

DATE MAILED: 05/13/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/843,126	ASTLES ET AL.	
	Examiner	Art Unit	
	Celia Chang	1625	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on *13 March 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1-72* is/are pending in the application.

4a) Of the above claim(s) *64-72* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-63* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☒ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

1. Applicant's election with traverse of group I, (claim 50, p.158, line 21, elected species in group I) in Paper No. 7, dated mar. 17, 2003 is acknowledged. The traversal is on the ground that the claims are drawn to Markush format thus variable ring size is not repugnant to principles of scientific classification. This is not found persuasive because applicants presented mere argument *without* factual evidence that the instant variable ring compounds share a substantial structural feature disclosed as being essential to the claimed utility.

Applicants attention is drawn to MPEP 803.02 restriction of Markush claims:"Broadly, unity of invention exists where compounds included within a Markush group (1)share a common utility ***and*** (2) share a substantial structural feature disclosed as being essential to that utility". The restriction was made based on that each different core structure have diverse utility for example, the pyrrolidinyl ring compounds are intermediates for making antibacterial (see US 5,342,844 col.16 example J), the seven membered ring compounds are antimicrobial (see CA128). Applicants presented mere arguments ***without*** factual evidence that diverse ring members responsible for diverse utility are obvious variants for the tryptase inhibition. Further, the specification on pages 147-148 disclosure support that this exclusive tryptase inhibitory activity is limited only to the piperidinyl compounds.

With respect to group IV, composition of multiple active ingredients are patentably distinct and unrelated to the other groups has been clearly delineated with factual evidence in the previous office action (see p.3 office action and citation of PTO-892). It was clearly evidenced by CA 132 that the combination of tryptase inhibitor and steroids would lead to synergistic decrease of mast cell activation while combination of tryptase inhibitor with adrenergic compounds (CA 110) would be counteracting on the smooth muscle relaxation. Therefore, not only combination of active ingredients is not obvious variants of single active ingredient composition but also such combination ***do not share any commonality*** of utility without specifically naming the class of active ingredients to be combined.

Applicants were advised that "Should applicant traverse on the ground that the groups and species are not patentably distinct, applicant should submit *evidence* or identify such evidence now of record showing the groups and species to be obvious variants or clearly admit

on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention." For which applicants provided neither evidence nor admission. Were admission of such obvious variation, then there could have been no patentability of all the claims over US 5,342,844 col.16 example J because example J is an N-benzyl protected compound of the claims while the claims are drawn to the alternative conventional N-benzoyl protected compounds. A clear establishment of prima facie obviousness over the variation of N-protecting compounds.

The requirement is still deemed proper and is therefore made FINAL.

Applicants' provisional election is confusing because both group I and group II were mentioned (see response p.4 last paragraph). Based on the species elected which is a piperidinyl compound of claim 50 (p.148 line 21), group I is examined. Claims 36-50, 52 and claims 1-35, and 51, 53-54 reading on n=2 compounds and compositions are prosecuted together with claims 55-63 to the extend of the elected compound for treating asthma. Claims 64-72 and the remaining subject matter of claims 1-35, 51, 53-54, 55-63 are withdrawn from consideration per 37 CFR 1.142(b).

2. Claims 1-49, 51-52, 55-63 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-49 employed the term "comprising" instead of consisting of for Markush elements which is improper (see MPEP2173.05(h)). Correction is required.

Claims 51-52 is self conflicting because claims 51-52 are pharmaceutical composition without quantitative limitation. A pharmaceutical composition by definition can not be either ineffective or toxic. Therefore, it is recommended that the term "therapeutically effective amount" be incorporated into the claims.

Claims 55-63 are ambiguous and confusing. It is unclear what the meets and bounds of the claims are by the terms "suffering from or subject to". A patient by definition has a disease which can manifest in form of pathology or symptom. It is unclear what does suffering from or subject to a condition which is ameliorate by inhibition of tryptase is referring to. Is the patient

sick or not. The claims are self conflicting and indefinite. It is recommended that the scope be particularly pointed out i.e. a method of treating asthma in a patient comprising administering to said patient a tryptase inhibitory effective amount of a compound of claim xxx.

3. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-5, 7-9, 11-19, 21-23, 26-27, 30-34, 36-38, 40-41, 44-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Pieper et al. US 5,442,064.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Determination of the scope and content of the prior art (MPEP §2141.01)

Pieper et al. '064 disclosed compounds having anti-aggregating of platelet activity. A compounds wherein the instant R3 is heterocycloalkyl is disclosed (see structural delineation for 162996-75-0 attached, which is corresponding to compound at col. 32, lines 28-29).

Ascertainment of the difference between the prior art and the claims (MPEP §2141.02)

Pieper et al. '064 disclosed all the elements of the claims **except** the heterocycle is linking to the other part of the molecule by a hetero-atom while the claims are drawn to carbon linked heterocycloalkyl. However, generically Pieper et al. '064 disclosed various linking position (see col. 42, claim 1) and exemplified in starting material/intermediates and final products of the variations in such position isomeric compounds (see structural delineation attached to reference).

Finding of prima facie obviousness---rational and motivation (MPEP§2142-2143)

One having ordinary skill in the art in possession of the Pieper et al. '064 reference is in possession of all the variations in position isomeric compounds of the exemplified compound named by CAS registry number 162996-75-0 **because** not only such equivalency in het-c or het N linker has been taught by the reference but also the many variations for such linker have be exemplified and enabled. The skilled artisan in possession of Pieper et al. '064 is in possession of how to make the broad disclosure through explicit exemplification and expects all the compounds embraced by the generic description would have similar anti-aggregating activity. In absence of unexpected results, there is nothing unobvious in choosing some among many. In re Lemin 141 USPQ 814.

Further, the broad scope encompassed heteroaryl instead of aryl for 162996-75-0 has also been taught and exemplified in analogous compounds (see aminomethylpyridyl example i.e col. 31 line 54), therefore, rendered the instant broad scope prima facie obvious since the clear exemplification of optional choices between aryl and heteroaryl would motivate one skilled in the art to pick and choose such attributes in making the generically taught alternative compounds of 162996-75-0 with heteroaroyl.

4. Claims 1-63 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims1-25 of U.S. Patent No. 2002/0045613 in view of Okumura et al. US 5,639,321 or Liebeschuetz et al. US 2002/0055522.

Claims 1-25 of US 2002/0045613 fully embraced the instant claims (see p.40-41 claim 1) since the instant claims have more limited scope but completely embraced by the copending claims. The copending claims differ from the instant claim in the species of claim 10 '613 did not have an aminomethyl substitution instead is a amidino substituted compound. Okumura '321 or Liebeschuetz '522 taught that in analogous compounds that in similar antithrombin compounds the substitution on the aryl ring with an aminomethyl group or a amidino group is an optional choice for such compounds without compromising the anticoagulation activity (see '321 col. 2 line 11, see '522 p.34, claim 28). One having ordinary skill in the anticoagulation compound art would be aware of all the pertinent art in the field. The above references placed the optional choices of substitutents on the aryl ring in the possession of artisan. The broad scope of US 2002/0045613 and the conventional teaching in the art of how to pick and choose variations of substituents on the aryl ring would motivate one skilled in the art to modify the species claim based on the generic claim of '613 employing the guidance well known in the art which are the instant claims.

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible

harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

5. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Celia Chang whose telephone number is 703-308-4702. The examiner can normally be reached on Monday through Thursday from 8:30 am to 5:00 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner can be reached by facsimile at (703) 308-7922 with courtesy voice message supra.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 703-308-1235.

Celia Chang
Primary Examiner
Art Unit 1625

OACS/Chang
May 6, 2003